PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: P. A. Billing-Medel, *et al.*

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For: REAGENTS AND METHODS USEFUL FOR DETECTING DISEASES OF THE LUNG

Examiner: G. Nickol

Group Art Unit: 1642

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2-27-03

DECLARATION OF PAULA N. FRIEDMAN, Ph.D.
UNDER 37 C.F.R. SECTION 1.132

Sir:

1. I am one skilled in the art of cancer diagnostics. I have a Ph.D and M.A. in Molecular Biology from Columbia University. I also have a B.A. in Biology from Dartmouth College.

2. I was a Postdoctoral Fellow in the Laboratory of Dr. Clay Siegall at the Pharmaceutical Research Institute at Bristol-Myers Squibb and an Assistant Pharmacologist, Department of Clinical Immunology & Biol. Therapy at the MD Anderson Cancer Center.

3. I have nine (9) years of research and development experience in the cancer diagnostic industry. Much of my work has involved the discovery and validation of novel cancer markers to improve the accuracy of diagnosing the onset of cancer. In fact, I am a named inventor on several U.S. Patents, all of which are related to the field of cancer diagnostics.

4. I also have authored numerous journal articles relating to cancer pathology, detection and metastasis (See Exhibit A).

5. I am one of the named inventors on the present application.

6. I have read and am familiar with the Office Action dated November 22, 2002 and the utility rejection under 35 U.S.C. Section 101 applied against the present application.

7. The identification of molecular markers to identify diseases in humans is extremely important. Several different categories of markers are known in the art. One such category of markers are those that are genes that are expressed in a tissue-specific manner but can appear in an inappropriate body compartment. The expression of a marker in a tissue or body compartment where their normal occurrence is very low or non-existent indicates that a disease has altered the marker so that has escaped from its host tissue. Examples of markers that fall into this category are prostate specific antigen (PSA) and carcinoembryonic antigen (CEA).

PSA is a member of the human tissue kallkrein gene family. PSA is normally secreted at high levels into the seminal fluid and is present in very low levels in the blood of men with normal prostates. However, in patients with diseases of the prostate, including benign prostatic hyperplasia (BPH) or adenocarcinoma of the prostate, the level of PSA is markedly elevated in the blood and is a strong indication of disease of the prostate.

Similarly, CEA is a normal component of the inner lining of the colon and is present stool and in blood at low levels in people without disease of the colon. However, in disease of the colon, including inflammatory bowel disease and adenocarcinoma of the colon, the concentration of CEA is markedly elevated in the blood plasma or serum of many patients and is an indicator of disease of that tissue (such as colorectal cancer).

8. I have reviewed the data illustrating CEA and PSA tissue specificity generated using the Incyte Lifeseq Gold database. The Incyte Lifeseq Gold database is a very large database of expressed sequence tags (ESTs). This is the database where the inventors of the present application discovered the markers that are the subject of the present application.

9. CEA is a tissue-specific marker that has been shown to be highly expressed in the gastrointestinal (GI) tract. Specifically, 61 out of 148 GI libraries express CEA whereas only 27 out of 1,144 other, non-GI tract libraries express this gene. Therefore, CEA is expressed approximately 17 times more in GI tissue when compared to the rest of the body.

10. Similarly, PSA is a tissue-specific marker that has been shown to be highly expressed in prostate. Specifically, 65 out of 79 prostate libraries (classified as male genitalia) express PSA whereas only 22 out of 1213 other, non-prostate libraries express this gene. Therefore, PSA is expressed approximately 45 times more in prostate when compared to the rest of the body.

11. To those skilled in the art, such as myself, PSA and CEA are well known tumor markers, which indicate cancer of the prostate (PSA) and GI tract (CEA) when the respective gene product is found in the blood sample of a patient.

12. As shown in the instant specification, LS147 is expressed only in lung tissue.

13. Clearly, LS147 is characteristic of a tissue specific marker and able to act as a cancer diagnostic, as evidenced by the specification.

14. Tissue-specific markers such as PSA and CEA are the most diagnostic tools in early oncology detection and are used on a daily basis. Further, the PSA gene product is utilized in screening, prognosis and monitoring prostate cancer patients by oncologists and is recommended that all men over the age of 40 be tested yearly with a PSA assay.

15. Based on the statistics in the Incyte database, LS147 is clearly a lung specific marker and, therefore, its use as a lung cancer marker is unquestionable. Therefore, to one of ordinary skill in the art, such as myself, the presence of LS147 outside of the lung would indicate cancer development of that tissue, just as the presence of CEA and PSA outside of their respective tissues indicates cancer of the colon and prostate, respectively.

16. I hereby declare that all statements made herein are of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Paula N. Friedman, Ph.D

2/5/03
Date

ATTACHMENT I

Publications:

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Bargonetti, J., Reynesdottir, I., **Friedman, P.N.,** and Prives, C. 1992. Wild-type p53 site-specific binding to cellular DNA is regulated by SV40 T antigen and mutant p53. Genes and Devel., 6, 1886-1898.

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Friedman, P.N., Chace, D.F., Trail, P.A., and Siegall, C.B.1993. Antitumor activity of the single-chain immunotoxin BR96 sFv-PE40 against established breast and lung tumor xenografts. J. of Immun., 150, 3054-3061.

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